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RESPONSE

I. Status of the Claims

Claim 1 has been cancelled without prejudice and without disclaimer. No claims have been amended. No new claims have been added.

Claims 2 and 4-7 are therefore presently pending in the case.

II. Rejection of Claims 1, 2 and 4-7 Under 35 U.S.C. § 101

The Action first rejects claims 1, 2 and 4-7 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

First, while Applicants in no way agree with the Examiner's position that claim 1 lacks a patentable utility, as claim 1 has been cancelled entirely without prejudice and without disclaimer solely in order to more rapidly progress the present case to allowance, the present rejection of claim 1 under 35 U.S.C. § 101 is rendered moot. The remainder of this section will therefore focus on claims 2 and 4-7.

The presently claimed sequence has clearly been described by Applicants as a GABA transporter protein (see, at least, the title of the application as originally filed, and page 2, lines 2-4 of the specification as originally filed). Additionally, Applicants respectfully point out that the presently claimed sequence shares **100% identity** at the amino acid level over the entire length of SEQ ID NO:2 with two sequences that are present in the leading scientific repository for biological sequence data (GenBank), which have been annotated by independent third party scientists *wholly unaffiliated with Applicants* as "Homo sapiens vesicular inhibitory amino acid transporter" (VIAAT; GenBank accession numbers AY044836 and NM_080552, alignments and GenBank reports provided in **Exhibit A**). Furthermore, three independent groups of scientists have confirmed Applicants' assertion that the presently claimed sequence, which is identical to the VIAAT protein described above, is a GABA transporter protein (Chessler *et al.*, *Diabetes* **51**:1763-1771, 2002 ("Chessler"); Jellali *et al.*, *J. Comp. Neurol.* **449**:76-87, 2002 ("Jellali"); and Geigerseder *et al.*, *Neuroendocrinology* **77**:314-323, 2003 ("Geigerseder"); abstracts provided in **Exhibit B**). Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55; **Exhibit C**), which have been set forth by the United States Patent and Trademark Office ("the USPTO"), clearly establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility, and under 35 U.S.C. § 112, first

paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility (see Section III, below), is not proper when a full length sequence (such as the presently claimed sequence) has a similarity score greater than 95% to a protein having a "well established utility". Therefore, as the present situation **exactly** tracks Example 10 of the Revised Interim Utility Guidelines Training Materials, the USPTO's **own** examination guidelines clearly indicate that the present claims meet the requirements of 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph (see Section III, below), and the present rejection of claims 2 and 4-7 should be withdrawn.

Applicants respectfully point out that whether or not the Chessler, Jellali, and Geigerseder references cited by Applicants above were available at the time of filing of the present application is not germane to the utility issue at hand. Applicants point to the Chessler, Jellali, and Geigerseder references **not** to evidence that these sequences were known in the art at the time the present application was filed, but, rather, to evidence that other skilled artisans have **confirmed** Applicants' assertion that the presently claimed sequence is a GABA receptor protein. Thus, the present claims meet the requirements of 35 U.S.C. § 101, and the present rejection of claims 2 and 4-7 should be withdrawn.

It has been well established that Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), and, thus, any questions concerning whether or not the present claims meet the requirements of 35 U.S.C. § 101 should have been laid to rest. Nevertheless, given the well established medical relevance of GABA receptors, Applicants point out that the present invention has a number of other patentable utilities, for example the utility of tracking expression of the presently claimed sequence. The specification details, at least at page 6, lines 2-4, that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776 (**Exhibits D-I**; copies of issued U.S. Patents not provided pursuant to requests from the USPTO). As the present sequences are specific markers of human chromosome 20 (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence

information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, *Science* **291**:1304, 2001; **Exhibit J**). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, *Science* **291**:1153, 2001; **Exhibit K**). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner discounts this asserted utility, stating that this utility is applicable to "any polynucleotide sequence" (the Action at page 4). This argument is flawed in at least two respects. First, Applicants respectfully point out that only expressed polynucleotide sequences can be used to track gene expression, not just "any polynucleotide sequence". Although the GABA receptor function of the presently claimed sequence has clearly been established, expression profiling does not even require a knowledge of the function of the particular nucleic acid on the chip - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types, such as cancer cell lines and normal controls. Skilled artisans already have used and continue to use sequences such as Applicants in gene chip applications without further experimentation. Second,

the Examiner seems to be confusing the requirements of a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, with that of a **unique** utility, which is clearly an improper standard. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991; "*Carl Zeiss*"):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Following directly from the quote above, an invention does not need to be the only way to accomplish a certain result. Thus, the question of whether or not **other** nucleic acid sequences can be used to assess gene expression patterns is completely irrelevant to the present utility inquiry. The **only** relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is an emphatic **no**. Importantly, the holding in the *Carl Zeiss* case is mandatory legal authority that essentially controls the outcome of the present case. This case, and particularly the cited quote, directly rebuts the Examiner's argument. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the USPTO. If every invention were required to have a unique utility, the USPTO would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Additionally, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Throughout the Action, the Examiner attempts to **narrowly** define the "general" class of the invention to include **only** those members that share the asserted utility, and then state that the asserted

utility is "general". Applicants respectfully point out that the "general" class with regard to the present invention is **all** nucleic acids. Applicants reiterate that **not** all nucleic acids are expressed - in fact, only 2-4% of all nucleotide sequences are expressed. Therefore, the question of whether the asserted utility is "specific", as opposed to "general", has **clearly** been laid to rest. Applicants note that the "general" class of the invention cannot be redefined to include **only** those nucleic acids that are expressed, as the Examiner is forced to do in order to support the allegation that the claimed nucleic acids lack a patentable utility. Thus, the Examiner's argument is completely improper and in clear defiance of established case law, and therefore is in no way whatsoever sufficient to overcome Applicants' assertion of utility. Therefore the present claims are clearly in compliance with 35 U.S.C. § 101.

As yet a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 3, lines 2-4, the present nucleotide sequence has a specific utility in "identification of protein coding sequences" and "mapping a unique gene to a particular chromosome". As described in the specification as originally filed at page 16, lines 22-24, the gene encoding the presently claimed sequences is present on "human chromosome 20 (see GENBANK accession no. AL133519)". In fact, alignment of the presently claimed sequence with GenBank accession number AL133519 (a genomic clone from human chromosome 20) shows that the human gene corresponding to the presently claimed sequence is dispersed on 2 exons of human chromosome 20 (alignment and first page of the GenBank report are presented in **Exhibit L**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 20 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (*supra*, at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the

requirements of 35 U.S.C. § 101.

Applicants once again respectfully remind the Examiner that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). As described in the specification as originally filed at page 3, lines 5-7, the claimed sequences "identify biologically verified exon splice junctions, as opposed to splice junctions that may have been bioinformatically predicted from genomic sequence alone". The specification also details that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics" (specification at page 11, lines 18-24). Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Once again, regarding the implication that "any polynucleotide sequence" (the Action at page 4) could be so used, Applicants first point out that only expressed sequences can be used in the identification of coding sequence, not just any nucleic acid. Applicants reiterate that the requirements of a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a **unique** utility, which is clearly an **improper** standard (*Carl Zeiss Stiftung v. Renishaw PLC, supra*). The fact that a small number of other nucleotide sequences could be used to map the protein coding regions in this specific region of chromosome 20 does not mean that the use of Applicants' sequence to map the protein coding regions of chromosome 20 is not a specific utility. Once again, the question of whether or not **other** nucleic acid sequences can be so used is completely irrelevant to the present utility inquiry. The **only** relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is once again an emphatic **no**. Applicants respectfully point out that in this case the Examiner is once again attempting to narrow the broad class of "any nucleic acid molecule" to include **only** polynucleotide sequences that are expressed in order to support the allegation that the claimed nucleic acids lack a patentable utility, which Applicants point out once again is improper under the law as well as the policy of the USPTO. Thus, the present claims clearly meet the requirements of

35 U.S.C. § 101.

It is important to note that it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Absent such evidence from the Examiner, as the skilled artisan would readily understand that the presently claimed sequence has a number of utilities, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Rather, as set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable (*State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

Furthermore, in *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the Patent and Trademark Office for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical

> inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted, emphasis added. As set forth above, the presently claimed sequence has a number of utilites, without the need for any further research. However, even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set

forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides; **Exhibits M-O**; copies of issued U.S. Patents not provided pursuant to requests from the USPTO), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples; **Exhibit P**; copies of issued U.S. Patents not provided pursuant to requests from the USPTO), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section III, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1, 2 and 4-7 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

III. Rejection of Claims 1, 2 and 4-7 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1, 2 and 4-7 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is

not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

First, while Applicants in no way agree with the Examiner's position that one skilled in the art would not know how to use the invention as set forth in claim 1, since claim 1 has been cancelled entirely without prejudice and without disclaimer solely in order to more rapidly progress the present case to allowance, the present rejection of claim 1 under 35 U.S.C. § 112, first paragraph is rendered moot. The remainder of this section will therefore focus on claims 2 and 4-7.

Applicants submit that as claims 2 and 4-7 have been shown to have "a specific, substantial, and credible utility", as detailed in section II above, the present rejection of claims 2 and 4-7 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1, 2 and 4-7 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. Rejection of Claim 1 Under 35 U.S.C. § 112, Second Paragraph

The Action next rejects claim 1 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention.

The Action rejects claim 1 as allegedly indefinite based on the term "stringent hybridization conditions", because the specific hybridization and washing conditions are not recited in the claim. Applicants stress that "a claim need not 'describe' the invention, such description being the role of the disclosure". *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). However, while Applicants submit that the term is sufficiently definite, as a number of stringent hybridization conditions are defined in the specification and would be known to those of skill in the art, solely in order to progress the case more rapidly toward allowance, claim 1 has been cancelled without prejudice and without disclaimer, thus rendering the present rejection moot.

As the rejection of claim 1 under 35 U.S.C. § 112, second paragraph, has been rendered moot, Applicants respectfully request withdrawal of this rejection.

V. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Wegert have any questions or comments,

or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

July 28, 2004
Date

David W. Hibler Reg. No. 41,071
Agent for Applicants

CUSTOMER NUMBER
24231

LEXICON GENETICS INCORPORATED
8800 Technology Forest Place
The Woodlands, TX 77381
(281) 863-3399

>AY044836 ACCESSION:AY044836 NID: gi 17975776 gb AY044836.1 Homo sapiens vesicular inhibitory amino acid transporter mRNA, complete cds
Length = 1592

Score = 1075 bits (2750), Expect = 0.0
Identities = 525/525 (100%), Positives = 525/525 (100%)
Frame = +3

```
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            MATLLRSKLSNVATSVSNKSQAKMSGMFARMGFQAATDEEAVGFAHCDDLDFEHRQGLQM
Sbjct: 6    MATLLRSKLSNVATSVSNKSQAKMSGMFARMGFQAATDEEAVGFAHCDDLDFEHRQGLQM 185

Query: 61   DILKAEGEPCGDEGAEAPVEGDIHYQRGSGAPLPPSGSKDQVGGGGEFGGHDKPKITAWE 120
            DILKAEGEPCGDEGAEAPVEGDIHYQRGSGAPLPPSGSKDQVGGGGEFGGHDKPKITAWE
Sbjct: 186  DILKAEGEPCGDEGAEAPVEGDIHYQRGSGAPLPPSGSKDQVGGGGEFGGHDKPKITAWE 365

Query: 121  AGWNVTNAIQGMFVLGLPYAILHGGYLGLFLIIFAAVVCCYTGKILIACLYEENEDGEVV 180
            AGWNVTNAIQGMFVLGLPYAILHGGYLGLFLIIFAAVVCCYTGKILIACLYEENEDGEVV
Sbjct: 366  AGWNVTNAIQGMFVLGLPYAILHGGYLGLFLIIFAAVVCCYTGKILIACLYEENEDGEVV 545

Query: 181  RVRDSYVAIANACCAPRFPTLGGRVVNVAQIIELVMTCILYVVVSGNLMYNSFPGLPVSQ 240
            RVRDSYVAIANACCAPRFPTLGGRVVNVAQIIELVMTCILYVVVSGNLMYNSFPGLPVSQ
Sbjct: 546  RVRDSYVAIANACCAPRFPTLGGRVVNVAQIIELVMTCILYVVVSGNLMYNSFPGLPVSQ 725

Query: 241  KSWSIIATAVLLPCAFLKNLKAVSKFSLLCTLAHFVINILVIAYCLSRARDWAWEKVKFY 300
            KSWSIIATAVLLPCAFLKNLKAVSKFSLLCTLAHFVINILVIAYCLSRARDWAWEKVKFY
Sbjct: 726  KSWSIIATAVLLPCAFLKNLKAVSKFSLLCTLAHFVINILVIAYCLSRARDWAWEKVKFY 905

Query: 301  IDVKKFPISIGIIVFSYTSQIFLPSLEGNMQQPSEFHCMMNWTHIAACVLKGLFALVAYL 360
            IDVKKFPISIGIIVFSYTSQIFLPSLEGNMQQPSEFHCMMNWTHIAACVLKGLFALVAYL
Sbjct: 906  IDVKKFPISIGIIVFSYTSQIFLPSLEGNMQQPSEFHCMMNWTHIAACVLKGLFALVAYL 1085

Query: 361  TWADETKEVITDNLPGSIRAVVNIFLVAKALLSYPLPFFAAVEVLEKSLFQEGSRAFFPA 420
            TWADETKEVITDNLPGSIRAVVNIFLVAKALLSYPLPFFAAVEVLEKSLFQEGSRAFFPA
Sbjct: 1086 TWADETKEVITDNLPGSIRAVVNIFLVAKALLSYPLPFFAAVEVLEKSLFQEGSRAFFPA 1265

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            CYSGDGRLKSWGLTLRCALVVFTLLMAIYVPHFALLMGLTGSLTGAGLCFLLPSLFHLRL
Sbjct: 1266 CYSGDGRLKSWGLTLRCALVVFTLLMAIYVPHFALLMGLTGSLTGAGLCFLLPSLFHLRL 1445

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            LWRKLLWHQVFFDVAIFVIGGICSVSGFVHSLEGLIEAYRTNAED
Sbjct: 1446 LWRKLLWHQVFFDVAIFVIGGICSVSGFVHSLEGLIEAYRTNAED 1580
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☐ **1:** AY044836. Homo sapiens vesi...[gi:17975776]

```
LOCUS       AY044836                1592 bp    mRNA    linear   PRI 24-JUN-2002
DEFINITION  Homo sapiens vesicular inhibitory amino acid transporter mRNA,
            complete cds.
ACCESSION   AY044836
VERSION     AY044836.1  GI:17975776
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 1592)
  AUTHORS   Chessler,S.D., Simonson,W.T., Sweet,I.R. and Hammerle,L.P.
  TITLE     Expression of the vesicular inhibitory amino acid transporter in
            pancreatic islet cells: distribution of the transporter within rat
            islets
  JOURNAL   Diabetes 51 (6), 1763-1771 (2002)
  MEDLINE   22027589
   PUBMED   12031963
REFERENCE   2  (bases 1 to 1592)
  AUTHORS   Chessler,S.D. and Gohlke,P.R.
  TITLE     Direct Submission
  JOURNAL   Submitted (10-JUL-2001) Medicine, University of Washington, UW
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Jul 27 2004 13:33:12

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ACCESSION NM_080552
VERSION NM_080552.2 GI:40806213
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Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 2581)
AUTHORS Geigerseder,C., Doepner,R., Thalhammer,A., Frungieri,M.B., Gamel-Didelon,K., Calandra,R.S., Kohn,F.M. and Mayerhofer,A.
TITLE Evidence for a GABAergic system in rodent and human testis: local GABA production and GABA receptors
JOURNAL Neuroendocrinology 77 (5), 314-323 (2003)
PUBMED 12806177
REFERENCE 2 (bases 1 to 2581)
AUTHORS Jellali,A., Stussi-Garaud,C., Gasnier,B., Rendon,A., Sahel,J.A., Dreyfus,H. and Picaud,S.
TITLE Cellular localization of the vesicular inhibitory amino acid transporter in the mouse and human retina
JOURNAL J. Comp. Neurol. 449 (1), 76-87 (2002)
PUBMED 12115694
REMARK GeneRIF: VIATT has been identified in horizontal cells of the adult outer retina in culture, either at their terminals or throughout the entire cell.
REFERENCE 3 (bases 1 to 2581)
AUTHORS Chessler,S.D., Simonson,W.T., Sweet,I.R. and Hammerle,L.P.
TITLE Expression of the vesicular inhibitory amino acid transporter in pancreatic islet cells: distribution of the transporter within rat islets
JOURNAL Diabetes 51 (6), 1763-1771 (2002)
PUBMED 12031963
REFERENCE 4 (bases 1 to 2581)
AUTHORS Kleiderlein,J.J., Nisson,P.E., Jessee,J., Li,W.B., Becker,K.G., Derby,M.L., Ross,C.A. and Margolis,R.L.
TITLE CCG repeats in cDNAs from human brain
JOURNAL Hum. Genet. 103 (6), 666-673 (1998)
PUBMED 9921901
REFERENCE 5 (bases 1 to 2581)
AUTHORS McIntire,S.L., Reimer,R.J., Schuske,K., Edwards,R.H. and Jorgensen,E.M.
TITLE Identification and characterization of the vesicular GABA transporter
JOURNAL Nature 389 (6653), 870-876 (1997)
PUBMED 9349821
COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from BI488536.1 and BC053582.1.

On Jan 13, 2004 this sequence version replaced gi:17999519.

Summary: The protein encoded by this gene is an integral membrane protein involved in gamma-aminobutyric acid (GABA) and glycine uptake into synaptic vesicles. The encoded protein is a member of amino acid/polyamine transporter family II.
COMPLETENESS: complete on the 3' end.

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1: Diabetes. 2002 Jun;51(6):1763-71.

Related Articles, Links

Expression of the vesicular inhibitory amino acid transporter in pancreatic islet cells: distribution of the transporter within rat islets.

Chessler SD, Simonson WT, Sweet IR, Hammerle LP.

Robert H. Williams Laboratory, Department of Medicine, University of Washington, Seattle, Washington 98195-7710, USA.
chessler@u.washington.edu

gamma-Aminobutyric acid (GABA) is stored in microvesicles in pancreatic islet cells. Because GAD65 and GAD67, which catalyze the formation of GABA, are cytoplasmic, the existence of an islet vesicular GABA transporter has been postulated. Here, we test the hypothesis that the putative transporter is the vesicular inhibitory amino acid transporter (VIAAT), a neuronal transmembrane transporter of GABA and glycine. We sequenced the human VIAAT gene and determined that the human and rat proteins share over 98% sequence identity. In vitro expression of VIAAT and immunoblotting of brain and islet lysates revealed two forms of the protein: an approximately 52-kDa and an approximately 57-kDa form. By immunoblotting and immunohistochemistry, we detected VIAAT in rat but not human islets. Immunohistochemical staining showed that in rat islets, the distribution of VIAAT expression parallels that of GAD67, with increased expression in the mantle. GABA, too, was found to be present in islet non-beta-cells. We conclude that VIAAT is expressed in rat islets and is more abundant in the mantle and that expression in human islets is very low or nil. The rat islet mantle differs from rat and human beta-cells in that it contains only GAD67 and relatively increased levels of VIAAT. Cells that express only GAD67 may require higher levels of VIAAT expression.

MeSH Terms:

- Amino Acid Sequence
- Animals
- Brain Chemistry
- Carrier Proteins/analysis
- Carrier Proteins/chemistry
- Carrier Proteins/genetics*
- Gene Expression*

- Glutamate Decarboxylase/analysis
- Glycine/metabolism
- Human
- Immunoblotting
- Immunohistochemistry
- Islets of Langerhans/chemistry*
- Isoenzymes/analysis
- Mice
- Molecular Sequence Data
- Rats
- Rats, Inbred BB
- Sequence Alignment
- Sequence Analysis
- Support, Non-U.S. Gov't
- Support, U.S. Gov't, P.H.S.
- Tissue Distribution
- gamma-Aminobutyric Acid/analysis
- gamma-Aminobutyric Acid/metabolism

Substances:

- Carrier Proteins
- Isoenzymes
- Viaat protein, rat
- gamma-Aminobutyric Acid
- Glycine
- GAD67 enzyme
- Glutamate Decarboxylase

Grant Support:

- DK17047/DK/NIDDK
- DK26190/DK/NIDDK
- K08 DK02944/DK/NIDDK

PMID: 12031963 [PubMed - indexed for MEDLINE]

Cellular localization of the vesicular inhibitory amino acid transporter in the mouse and human retina.

Jellali A, Stussi-Garaud C, Gasnier B, Rendon A, Sahel JA, Dreyfus H, Picaud S.

Laboratoire de Physiopathologie Cellulaire et Moleculaire de la Retine, INSERM EMI-99-18, Universite Louis Pasteur, 1 Place de l'Hopital, 67091 Strasbourg Cedex, France.

Horizontal cells are classically thought to mediate lateral inhibition by gamma-aminobutyric acid (GABA)-transporter mediated release. In the mammalian retina, however, GABA uptake and cloned GABA transporter were not detected in horizontal cells. Furthermore, the vesicular inhibitory amino acid transporter (VIAAT or VGAT) that loads GABA and glycine into synaptic vesicles was reported recently to be expressed in horizontal cells. To further assess synaptic transmission in mammalian horizontal cells, we examined the subcellular distribution of VIAAT in mouse and human retina by confocal microscopy with specific cell markers. VIAAT was observed in the mouse outer plexiform layer as punctate structures that localized in calbindin-positive horizontal cells. These structures were in close apposition with synaptophysin-, PSD-95-, dystrophin-, and bassoon-immunopositive photoreceptor terminals, suggesting that VIAAT is localized in horizontal cell tips at photoreceptor terminals. VIAAT-positive puncta were also in apposition to lectin-labeled cone terminals or dendrites of PKCalpha-immunopositive rod bipolar cells, indicating that VIAAT is expressed in horizontal cell tips at both rod and cone terminals. By contrast, only a very few puncta were observed in the human outer plexiform layer, whereas the inner plexiform layer remained labeled as in the mouse retina. When using adult human retinal cells in culture, horizontal cells identified by parvalbumin immunostaining were found to contain VIAAT, either at their terminals or throughout the entire cell similarly as in syntaxin-immunopositive cells. These differences between human retinal tissue and cultured cells were attributed to VIAAT degradation in postmortem retinal tissue. VIAAT localization in mouse and human horizontal cells further support the role of inhibitory transmitters in lateral inhibition at the photoreceptor terminals.

MeSH Terms:

- Animals
- Carrier Proteins/analysis*
- Carrier Proteins/ultrastructure
- Cells, Cultured
- Human
- Mice
- Protein Transport/physiology
- Retina/chemistry*
- Retina/ultrastructure
- Support, Non-U.S. Gov't
- gamma-Aminobutyric Acid/secretion

Substances:

- Carrier Proteins
- Viaat protein, rat
- gamma-Aminobutyric Acid

PMID: 12115694 [PubMed - indexed for MEDLINE]

1: Neuroendocrinology. 2003 May;77(5):314-23. Related Articles, Links

Evidence for a GABAergic system in rodent and human testis: local GABA production and GABA receptors.

Geigerseder C, Doepner R, Thalhammer A, Frungieri MB, Gamel-Didelon K, Calandra RS, Kohn FM, Mayerhofer A.

Anatomisches Institut der Universitat Munchen, Munchen, Deutschland.

The major neurotransmitter of the central nervous system, gamma-aminobutyric acid (GABA), exerts its actions through GABA(A), GABA(B) and GABA(C) receptors. GABA and GABA receptors are, however, also present in several non-neural tissues, including the endocrine organs pituitary, pancreas and testis. In the case of the rat testis, GABA appears to be linked to the regulation of steroid synthesis by Leydig cells via GABA(A) receptors, but neither testicular sources of GABA, nor the precise nature of testicular GABA receptors are fully known. We examined these points in rat, mouse, hamster and human testicular samples. RT-PCR followed by sequencing showed that the GABA-synthesizing enzymes glutamate decarboxylase (GAD) 65 and/or GAD67, as well as the vesicular GABA transporter vesicular inhibitory amino acid transporter (VIAAT/VGAT) are expressed. Testicular GAD in the rat was shown to be functionally active by using a GAD assay, and Western blot analysis confirmed the presence of GAD65 and GAD67. Interstitial cells, most of which are Leydig cells according to their location and morphological characteristics, showed positive immunoreaction for GAD and VIAAT/VGAT proteins. In addition, several GABA(A) receptor subunits (alpha1-3, beta1-3, gamma1-3), as well as GABA(B) receptor subunits R1 and R2, were detected by RT-PCR. Western blot analysis confirmed the results for GABA(A) receptor subunits beta2/3 in the rat, and immunohistochemistry identified interstitial Leydig cells to possess immunoreactive GABA(A) receptor subunits beta2/3 and alpha1. The presence of GABA(A) receptor subunit alpha1 mRNA in interstitial cells of the rat testis was further shown after laser microdissection followed by RT-PCR analysis. In summary, these results describe molecular details of the components of an intratesticular GABAergic system expressed in the endocrine compartment of rodent and human testes. While the physiological significance of this peripheral neuroendocrine system conserved throughout species remains to be elucidated, its mere presence in humans suggests the possibility that clinically used drugs might be able to interfere with testicular function. Copyright 2003 S. Karger

AG, Basel

MeSH Terms:

- Adult
- Animals
- Gene Expression
- Glutamate Decarboxylase/metabolism
- Human
- Immunohistochemistry
- Leydig Cells/metabolism
- Male
- Mice
- Mice, Inbred BALB C
- RNA/isolation & purification
- Rats
- Rats, Sprague-Dawley
- Rats, Wistar
- Receptors, GABA/classification
- Receptors, GABA/genetics
- Receptors, GABA/metabolism*
- Reverse Transcriptase Polymerase Chain Reaction
- Support, Non-U.S. Gov't
- Testis/metabolism*
- gamma-Aminobutyric Acid/genetics
- gamma-Aminobutyric Acid/metabolism*

Substances:

- Receptors, GABA
- gamma-Aminobutyric Acid
- RNA
- Glutamate Decarboxylase

PMID: 12806177 [PubMed - indexed for MEDLINE]

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characterize the protein. A starting material that can only be used to produce a final product does not have a substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case none of the proteins that are to be produced as final products resulting from processes involving the claimed cDNA have asserted or identified specific and substantial utilities. The research contemplated by Applicants to characterize potential protein products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of the protein itself or the mechanisms in which the protein is involved does not define a "real world" context of use. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the cDNA compounds such that another non-asserted utility would be well established for the compounds.

Claim 1 is also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Example 10: <u>DNA Fragment encoding a Full Open Reading Frame (ORF)</u>

Specification: The specification discloses that a cDNA library was prepared from human kidney epithelial cells and 5000 members of this library were

sequenced and open reading frames were identified. The specification discloses a Table that indicates that one member of the library having SEQ ID NO: 2 has a high level of homology to a DNA ligase. The specification teaches that this complete ORF (SEQ ID NO: 2) encodes SEQ ID NO: 3. An alignment of SEQ ID NO: 3 with known amino acid sequences of DNA ligases indicates that there is a high level of sequence conservation between the various known ligases. The overall level of sequence similarity between SEQ ID NO: 3 and the consensus sequence of the known DNA ligases that are presented in the specification reveals a similarity score of 95%. A search of the prior art confirms that SEQ ID NO: 2 has high homology to DNA Ligase encoding nucleic acids and that the next highest level of homology is to alpha-actin. However, the latter homology is only 50%. Based on the sequence homologies, the specification asserts that SEQ ID NO: 2 encodes a DNA ligase.

Claim 1: An isolated and purified nucleic acid comprising SEQ ID NO: 2.

Analysis: The following analysis includes the questions that need to be asked according to the guidelines and the answers to those questions based on the above facts:

1) Based on the record, is there a "well established utility" for the claimed invention? Based upon applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO: 2 encodes a DNA ligase. Further, DNA ligases have a well-established use in the molecular biology art based on this class of protein's ability to ligate DNA. Consequently the answer to the question is yes.

Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed. In order to determine whether the claimed invention has a well-established utility the examiner must determine that the invention has a specific, substantial and credible utility that would have been readily apparent to one of skill in the art. In this case SEQ ID NO: 2 was shown to encode a DNA ligase that the artisan would have recognized as having a specific, substantial and credible utility based on its enzymatic activity.

Thus, the conclusion reached from this analysis is that a 35 U.S.C. § 101 rejection and a 35 U.S.C. § 112, first paragraph, utility rejection should not be made.

Example 11: Animals with Uncharacterized Human Genes

Specification: Kidney cells from a patient with Polycystic Kidney (PCK) Disease have been used to make a cDNA library. From this library 8000 nucleotide "fragments" have been sequenced but not yet used to express proteins in a transformed host cell nor have they been characterized in any other way. The 50 longest fragments, SEQ ID NO: 1-50, respectively, have been used to make transgenic mice. None of the 50 lines of mice have developed Polycystic Kidney Disease to date. The asserted utility is the use of the mice to research human genes from diseased human kidneys. The disease is inheritable, but chromosomal loci have not yet been identified. Neither the absence or presence of a specific protein has been identified with the disease condition.

Query= SEQ ID NO:1
(1578 letters)

Sequences producing significant alignments:	Score (bits)	E Value
AL133519.28.1.96299	2361	0.0

>AL133519.28.1.96299
Length = 96299

Score = 2361 bits (1191), Expect = 0.0
Identities = 1191/1191 (100%)
Strand = Plus / Plus

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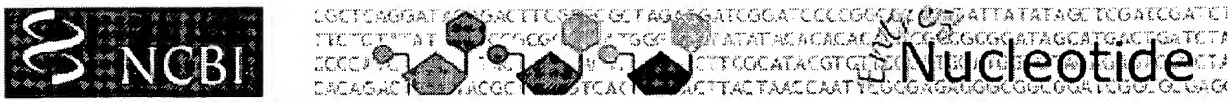


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DEFINITION  Human DNA sequence from clone RP11-122O1 on chromosome 20 Contains
            a novel gene encoding a protein orthologous to the mouse vesicular
            inhibitory amino acid transporter (VIAAT), the ACTR5 gene for  ARP5
            actin-related protein 5 homolog (yeast) and 3 CpG islands, complete
            sequence.
ACCESSION   AL133519
VERSION     AL133519.28  GI:10045268
KEYWORDS    HTG; Actin; ACTR5; amino acid transporter; CpG island.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 96299)
  AUTHORS   Peck,A.
  TITLE     Direct Submission
  JOURNAL   Submitted (02-JUL-2002) Wellcome Trust Sanger Institute, Hinxton,
            Cambridgeshire, CB10 1SA, UK. E-mail enquiries:
            humquery@sanger.ac.uk Clone requests: clonerequest@sanger.ac.uk
COMMENT     On Sep 9, 2000 this sequence version replaced gi:9988106.
            During sequence assembly data is compared from overlapping clones.
            Where differences are found these are annotated as variations
            together with a note of the overlapping clone name. Note that the
            variation annotation may not be found in the sequence submission
            corresponding to the overlapping clone, as we submit sequences with
            only a small overlap as described above.
            The following abbreviations are used to associate primary accession
            numbers given in the feature table with their source databases:
            Em:, EMBL; Sw:, SWISSPROT; Tr:, TREMBL; Wp:, WORMPEP; Information
            on the WORMPEP database can be found at
            http://www.sanger.ac.uk/Projects/C_elegans/wormpep This sequence
            was generated from part of bacterial clone contigs of human
            chromosome 20, constructed by the Sanger Centre Chromosome 20
            Mapping Group.  Further information can be found at
            http://www.sanger.ac.uk/HGP/Chr20
            This sequence was finished as follows unless otherwise noted: all
            regions were either double-stranded or sequenced with an alternate
            chemistry or covered by high quality data (i.e., phred quality >=
            30); an attempt was made to resolve all sequencing problems, such
            as compressions and repeats; all regions were covered by at least
            one plasmid subclone or more than one M13 subclone; and the
            assembly was confirmed by restriction digest. RP11-122O1 is from
            the library RPCI-11.1 constructed by the group of Pieter de Jong.
            For further details see
            http://www.chori.org/bacpac/home.htm
            VECTOR: pBACe3.6
            -------------- Genome Center
            Center: Wellcome Trust Sanger Institute
            Center code: SC
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